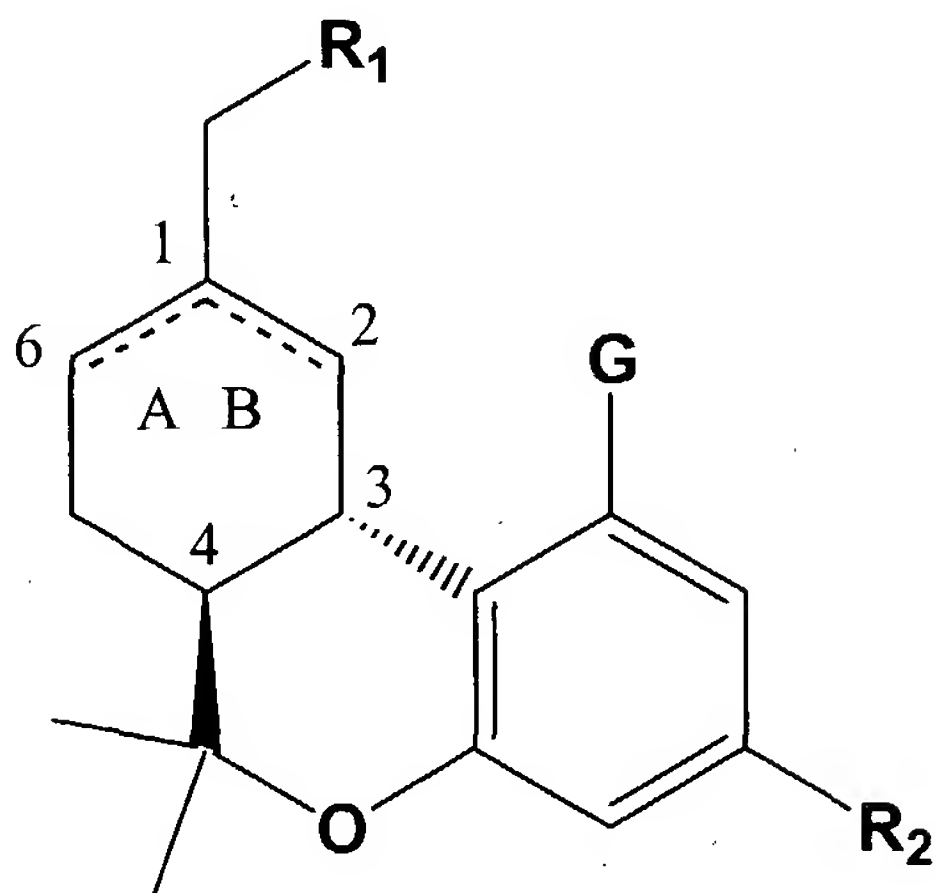


THE CLAIMS

What is claimed is:

1. A compound of the general Formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B indicates an optional 1(2) or 6(1) double bond,

R₁ is

A) R₃ where R₃ is selected from the group consisting of

- a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms interrupted by 1-3 heteroatoms; or
- b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from
 - i) C₁₋₆ alkyl,
 - ii) C₁₋₆ alkoxy,
 - iii) C₁₋₆ alkylthio,
 - iv) halo,

- v) carboxyl,
- vi) $-\text{CO}_2\text{-C}_{1-4}$ alkyl,
- vii) keto,
- viii) nitro,
- ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety having from 5-20 atoms comprising one or two ringed structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R_3 above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R_3 above; or

D) an ether $-\text{OR}_3$ wherein R_3 is as defined above;

G is (a) halogen, (b) $\text{C}_1\text{-C}_6$ alkyl, or (c) $-\text{OR}$ wherein R is (a') $-\text{R}''$, wherein R'' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl optionally containing a terminal $-\text{OR}'''$ or $-\text{OC}(\text{O})\text{R}'''$ moiety wherein R''' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, or (b') $-\text{C}(\text{O})\text{R}'''$ wherein R''' is as previously defined, and

R₂ is (a) $\text{C}_1\text{-C}_{12}$ alkyl, (b) $-\text{OR}''''$, in which R'''' is a straight chain or branched $\text{C}_2\text{-C}_9$ alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) $-(\text{CH}_2)_n\text{OR}'''$ wherein n is an integer of 1 to 7 and R''' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl; with the proviso that **R₁** is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue.

2. The compound according to claim 1 wherein **R₁** is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ring structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with at least one substituent selected from the group consisting of lower alkyl, halogen,

nitro, cyano, -SR^{'''}, -NHR^{'''}, -N(R^{'''})₂, -OR^{'''}, -COR^{'''}, -C(O)OR^{'''} or NH-COR^{'''} moiety wherein R^{'''} is hydrogen or C₁-C₆ alkyl.

3. The compound according to claim 1 wherein **R**₁ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazoliny, a morpholino, a piperidyl, a piperaziny, a pyrazolyl, a pyrrolyl, a pyrrolidiny, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

4. The compound according to claim 1 wherein **R**₁ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazoliny, or 4-methylpiperidiny.

5. The compound according to claim 1 wherein A-----B is a 6(1) double bond and **G** is -OH or lower acyloxy.

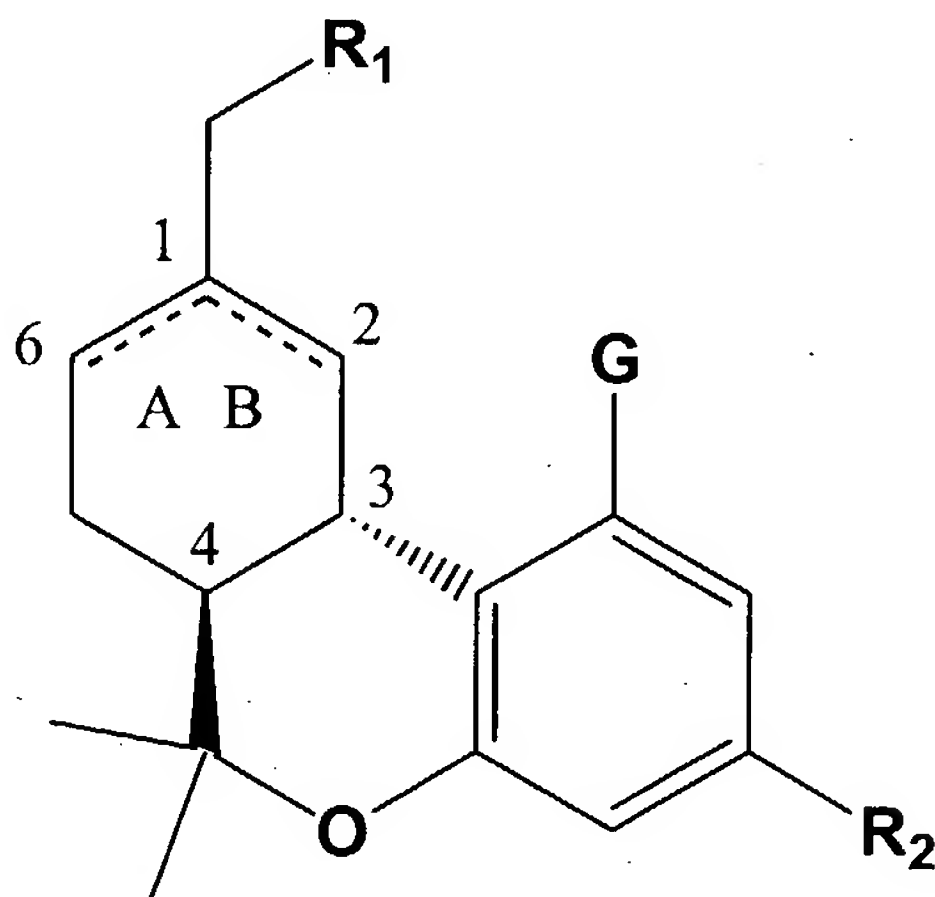
6. The compound according to claim 5 wherein **R**₂ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein **R**₁ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido, benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

7. The compound according to claim 6 wherein **R**₁ is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

8. The compound according to claim 1 wherein A----B is absent and **G** is -OH or lower alkoxy.

9. The compounds according to claim 1 selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(pyrazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanylmethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-piperidinopiperidine methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-methylpiperidine methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran.

10. A pharmaceutical composition comprising as an active ingredient a compound of the general formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A----B indicates an optional 1(2) or 6(1) double bond,

R₁ is

A) **R₃** where **R₃** is selected from the group consisting of

a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms interrupted by 1-3 heteroatoms; or
b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from

- i) C₁₋₆ alkyl,
- ii) C₁₋₆ alkoxy,
- iii) C₁₋₆ alkylthio,
- iv) halo,
- v) carboxyl,
- vi) -CO₂-C₁₋₄ alkyl,
- vii) keto,
- viii) nitro,
- ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety comprising one or two ringed structures wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R₃ above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R₃ above; or

D) an ether -OR₃ wherein R₃ is as defined above;

G is (a) halogen, (b) C₁-C₆ alkyl, or (c) -OR wherein R is (a') -R'', wherein R'' is hydrogen or C₁-C₆ alkyl optionally containing a terminal -OR''' or -OC(O)R''' moiety wherein R''' is hydrogen or C₁-C₆ alkyl, or (b') -C(O)R''' wherein R''' is as previously defined, and

R₂ is (a) C₁-C₁₂ alkyl, (b) -OR^{'''}, in which R^{'''} is a straight chain or branched C₂-C₉ alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) -(CH₂)_nOR^{'''} wherein n is an integer of 1 to 7 and R^{'''} is hydrogen or C₁-C₆ alkyl; with the proviso that **R**₁ is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue; together with a pharmaceutically acceptable diluent or carrier.

11. The composition according to claim 10 wherein **R**₁ is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with at least one substituent selected from the group consisting of lower alkyl, halogen, nitro, cyano, -SR^{'''}, -NHR^{'''}, -N(R^{'''})₂, -OR^{'''}, -COR^{'''}, -C(O)OR^{'''} or NH-COR^{'''} moiety wherein R^{'''} is hydrogen or C₁-C₆ alkyl.

12. The composition according to claim 10 wherein **R**₁ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazolinyl, a morpholino, a piperidyl, a piperazinyl, a pyrazolyl, a pyrrolyl, a pyrrolidinyl, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

13. The composition according to claim 10 wherein **R**₁ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazolinyl, or 4-methylpiperidinyl.

14. The composition according to claim 10, wherein A-----B is a 6(1) double bond, and **G** is -OH or lower acyloxy.

15. The composition according to claim 14 wherein **R**₂ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein **R**₁ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-

imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido, benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

16. The composition according to claim 15 wherein **R₁** is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

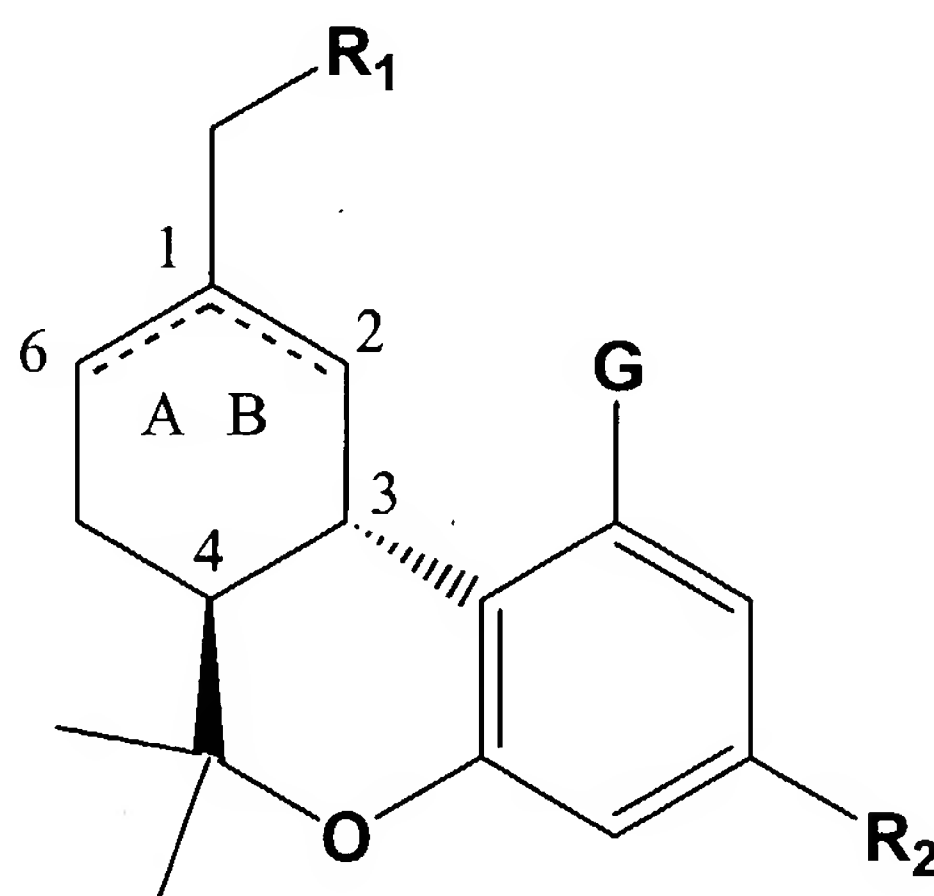
17. The composition according to claim 10 wherein A-----B is absent and G is OH or a lower alkoxy group.

18. The composition according to claim 10 wherein the active ingredient is selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(pyrazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanylmethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-piperidinopiperidinomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(4-methylpiperidine methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran.

19. The composition according to claim 10 wherein the carrier or diluent is an aqueous cosolvent solution comprising a pharmaceutically acceptable cosolvent, a micellar solution prepared with natural or synthetic ionic or non-ionic surfactants, or a combination of such cosolvent and micellar solutions.

20. The composition according to claim 19 wherein the carrier is (a) a solution of ethanol, a surfactant, and water or (b) an emulsion comprising a triglycerides, lecithin, glycerol, an emulsifier, an antioxidant, and water.

21. A method for treating or preventing inflammatory diseases or disorders, damage resulting from ischemia, injuries to the central nervous system and neurodegenerative disorders, pain, autoimmune diseases, cardiovascular disorders, or drug abuse, tolerance or dependence, by administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formula (I):



having the (3S,4S) configuration and being essentially free of the (3R,4R) enantiomer, wherein A-----B indicates an optional 1(2) or 6(1) double bond, **R₁** is

A) **R₃** where **R₃** is selected from the group consisting of

- a) a linear or branched, saturated or unsaturated, carbon side chain comprising 1-8 carbon atoms interrupted by 1-3 heteroatoms; or
- b) a saturated or unsaturated cyclic moiety or an aromatic or heterocyclic moiety having from 5-20 atoms comprising one or two-ringed structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from

- i) C₁₋₆ alkyl,
- ii) C₁₋₆ alkoxy,
- iii) C₁₋₆ alkylthio,

- iv) halo,
- v) carboxyl,
- vi) $-\text{CO}_2\text{-C}_{1-4}$ alkyl,
- vii) keto,
- viii) nitro,
- ix) a saturated or unsaturated cyclic moiety, or an aromatic or a heterocyclic moiety comprising one or two ringed structures wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; wherein each ring optionally is further substituted with one or more groups selected from i)-viii) as defined above;

B) an amine or an amide substituted with at least one substituent as defined in R_3 above;

C) a thiol, a sulfide, a sulfoxide, a sulfone, a thioester or a thioamide optionally substituted with one substituent as defined in R_3 above; or

D) an ether $-\text{OR}_3$ wherein R_3 is as defined above;

G is (a) halogen, (b) $\text{C}_1\text{-C}_6$ alkyl, or (c) $-\text{OR}$ wherein R is (a') $-\text{R}''$, wherein R'' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl optionally containing a terminal $-\text{OR}'''$ or $-\text{OC}(\text{O})\text{R}'''$ moiety wherein R''' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, or (b') $-\text{C}(\text{O})\text{R}'''$ wherein R''' is as previously defined, and

R₂ is (a) $\text{C}_1\text{-C}_{12}$ alkyl, (b) $-\text{OR}''''$, in which R'''' is a straight chain or branched $\text{C}_2\text{-C}_9$ alkyl which may be substituted at the terminal carbon atom by a phenyl group, or (c) $-(\text{CH}_2)_n\text{OR}'''$ wherein n is an integer of 1 to 7 and R''' is hydrogen or $\text{C}_1\text{-C}_6$ alkyl; with the proviso that **R₁** is other than a heterocyclic moiety having a labile hydrogen atom so that said moiety acts as a carboxylic acid analogue.

22. The method according to claim 21 wherein **R₁** is a saturated or unsaturated cyclic moiety, an aromatic moiety or a heterocyclic moiety having from 5-20 atoms comprising one or two-ring structures, wherein each ring comprises 3-8 carbons interrupted by 0-4 heteroatoms, said heteroatoms each independently selected from the group consisting of N, O, and S; optionally further substituted with

at least one substituent selected from the group consisting of lower alkyl, halogen, nitro, cyano, -SR^{'''}, -NHR^{'''}, -N(R^{'''})₂, -OR^{'''}, -COR^{'''}, -C(O)OR^{'''} or NH-COR^{'''} moiety wherein R^{'''} is hydrogen or C₁-C₆ alkyl.

23. The method according to claim 21 wherein **R**₁ is a heterocyclic moiety selected from the group consisting of an imidazolyl, an imidazoliny, a morpholino, a piperidyl, a piperaziny, a pyrazolyl, a pyrrolyl, a pyrrolidiny, a triazolyl, and a tetrazolyl, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures.

24. The method according to claim 21 wherein **R**₁ is imidazolyl, pyrazolyl, 2-methyl thio-2-imidazoliny, or 4-methylpiperidiny.

25. The method according to claim 21 wherein A-----B is a 6(1) double bond, and G is -OH or lower acyloxy.

26. The method according to claim 25 wherein **R**₂ is 1,1-dimethylheptyl or 1,2-dimethylheptyl and wherein **R**₁ is selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, tetrahydropyridine, pyrazoline, oxazoline, pyrrolidine, imidazoline, 2-thio-imidazole, 2-methylthio-imidazoline, 4-methyl-2-imidazoline, 4,4-dimethyl-2-imidazoline, methyl sulfide, methylsulfoxide, acetamido, benzamide, cyano, 1,2,4-triazole, 1,3,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, thiophene, phenyl, morpholine, thiomorpholine, thiazolidine, glycerol, piperazine, piperidine and tetrahydropyran, optionally further substituted wherein the substituent is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, keto, carboxy, or nitro, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy and C₁₋₆ alkylthio are intended to include saturated and unsaturated linear, branched and cyclic structures

27. The method according to claim 26 wherein **R**₁ is imidazole, pyrazole, 2-methyl thio-2-imidazoline, or 4-methylpiperidine.

28. The method according to claim 21 wherein A-----B is absent and **G** is -OH or lower acyloxy.

29. The method according to claim 21 wherein said compound is selected from the group consisting of: (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(imidazolo methyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(pyrazolomethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy-9-(1H-imidazol-2-ylsulfanylmethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S)-6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy -9-(4-piperidinopiperidinemethyl)-6a,7,10,10a-tetrahydro-6H-dibenzo[b,d]pyran; (+)-(3S,4S) -6,6-Dimethyl-(1,1-dimethylheptyl)-1-hydroxy -9-(4-methylpiperidine methyl)-6a,7,10,10a- tetrahydro-6H- dibenzo[b,d]pyran.

30. The method according to claim 21 wherein said compound is administered in a manner to protect against excitatory amino acid-mediated neurotoxicity.

31. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with tolerance or dependence to opioids, cocaine, psychostimulants or alcohol.

32. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with neural injury due to edema, neural injury due to cerebral ischemia, neural injury due to head trauma, poisoning of the central nervous system, cardiac arrest, stroke, optic neuropathy, or spinal cord injury.

33. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with epilepsy, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or Alzheimer's disease.

34. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with chronic, neuropathic or other pain.

35. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Graves disease, Hashimoto's thyroiditis, or inflammatory bowel.

36. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with myocardial infarction, atheroma, unstable angina, restenosis, or ischemic damage to the cardiovascular system.

37. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with ischemic and/or inflammatory damage to body organs including the lungs, liver, kidney or joints related to pulmonary, hepatic, or renal ischemias, rheumatoid arthritis or septic shock.

38. The method according to claim 21 which comprises administering said compound to a patient who exhibits the symptoms associated with glaucoma, retinal degeneration or emesis.

39. The method according to claim 21 wherein the daily dosage of said compound is between 0.01 and 25 mg/kg.

40. The method according to claim 21 wherein the composition is administered orally, parenterally, intravenously, intramuscularly, intralesionally, subcutaneously, transdermally, intratechally, rectally or intranasally.